Design, synthesis and cytotoxicity of pyrano[4,3-*b*]indol-1(5*H*)-ones: A hybrid pharmacophore approach via gold catalyzed cyclization

Chandrasekar Praveen, D. Babu Ananth

PII: S0960-894X(16)30320-1
DOI: http://dx.doi.org/10.1016/j.bmcl.2016.03.087
Reference: BMCL 23730

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 31 January 2016
Revised Date: 16 March 2016
Accepted Date: 25 March 2016

Please cite this article as: Praveen, C., Babu Ananth, D., Design, synthesis and cytotoxicity of pyrano[4,3-*b*]indol-1(5*H*)-ones: A hybrid pharmacophore approach via gold catalyzed cyclization, *Bioorganic & Medicinal Chemistry Letters* (2016), doi: http://dx.doi.org/10.1016/j.bmcl.2016.03.087

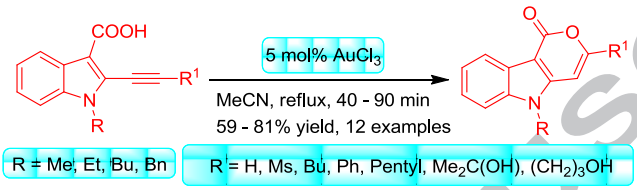
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Design, synthesis and cytotoxicity of pyrano[4,3-*b*]indol-1(5*H*)-ones: A hybrid pharmacophore approach via gold catalyzed cyclization

Leave this area blank for abstract info.

Chandrasekar Praveen[a,*] and D Babu Ananth[b]



Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

Design, synthesis and cytotoxicity of pyrano[4,3-*b*]indol-1(5*H*)-ones: A hybrid pharmacophore approach via gold catalyzed cyclization

Chandrasekar Praveen[a,*] and D Babu Ananth[b]

[a]*Functional Materials Division, CSIR-Central Electrochemical Research Institute (CSIR-CECRI), Karaikudi-630003, Tamil Nadu, India*
[b]*Pharmaceutical Analysis Department, EGS Pillay College of Pharmacy, Nagapattinam-611002, Tamil Nadu, India*

ARTICLE INFO

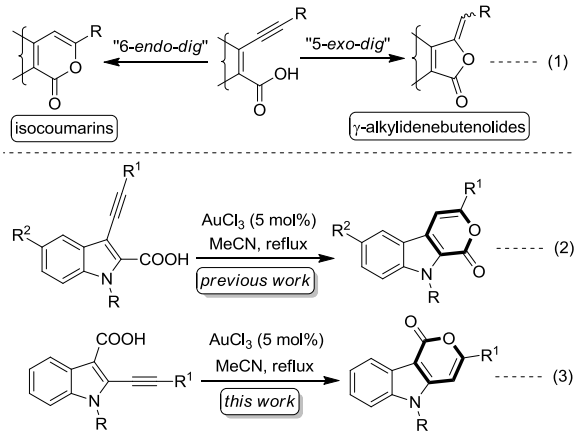
Article history:
Received
Revised
Accepted
Available online

Keywords:
Pyranoindolones
Cycloisomerization
Gold catalysis
Cytotoxicity
Molecular docking

ABSTRACT

Reported herein is the gold(III)-catalyzed 6-*endo-dig* cycloisomerization of 2-alkynyl-indole-3-carboxylic acids to form pyrano[4,3-*b*]indol-1(5*H*)-ones, which are pharmaceutically important structural motifs. The hitherto unknown substrates required for this methodology were conveniently synthesized in five steps with good overall yields. The utility of this new cycloisomerization is demonstrated by the excellent regioselectivity obtained using a range of substrates. The mildness of the method allowed functional group compatibility towards hydroxyl tether, displaying exquisite chemoselectivity. All the synthesized compounds were screened for their tumor cell growth inhibitory activity against human cervix adenocarcinoma (HeLa). Compound **7d** emerged as the most active (IC_{50} = 0.69 μM) among the tested series compared to the standard *cis*-platin (IC_{50} = 0.08 μM).

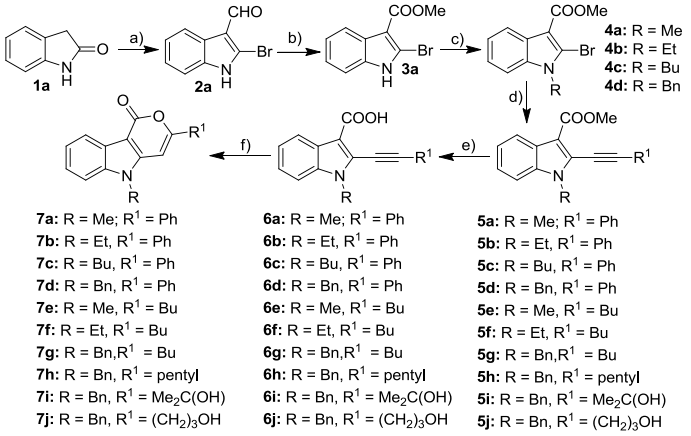
Isocoumarin and pyranone cores are structural motifs that are featured in a large family of natural products[1] and pharmaceutical agents.[2] Among several synthetic avenues, cyclization of acetylenic acids are one of the modern approaches for the synthesis of isocoumarins.[3,4] This cyclization as allowed by Baldwin's rule often leads to two regioisomeric products; isocoumarins and γ-alkylidenebutenolides via 6-*endo-dig* and 5-*exo-dig* attack respectively (Scheme 1, eq 1). A plethora of Lewis and Brønsted acid catalysts have been developed for the cyclization of acetylenic acids, the results in most cases offer no regioselectivity and lead to the formation of both γ- and δ-lactones.[3a-3t] On the other hand, there are only very few reports appeared for the selective synthesis of either δ-lactone[3n-3x] or γ-lactone.[4] Therefore, the regioselective synthesis of one among the two heterocycles appeared attractive from a synthetic chemist perspective. As part of our[5] ongoing interest in homogeneous gold catalysis[6a] for the construction of novel heterocycles,[6b] we have previously reported the $AuCl_3$[7] catalyzed 6-*endo-dig* cycloisomerization of 3-alkynyl-indole-2-carboxylic acids leading to biologically active pyrano[3,4-*b*]indol-1(9*H*)-ones (Scheme 1, eq 2).[5h] As a logical speculation, we envisaged the synthesis of corresponding positional isomer, pyrano[4,3-*b*]indol-1(5*H*)-ones by utilising 2-alkynyl-indole-3-carboxylic acids. The synthesis of these compounds has scarcely been investigated. Some rare examples include $[(Cp^*RhCl_2)_2]/Cu(OAc)_2$ catalyzed oxidative coupling of indole-3-carboxylic acid with internal alkynes,[8a] Pd(II)-catalyzed oxidative coupling of indole-3-carboxylic acids with styrenes,[8b, 9] CuI catalyzed tandem cross-coupling/cyclization of iodo-heteroarenes with terminal acetylenes[10a] and organocatalyzed CO_2 trapping of alkynyl indoles.[10b] However, the substrate scope in these protocols was limited. To this end, a gold catalytic protocol that accomplishes the cycloisomerization of 2-alkynyl-indole-3-carboxylic acids remains to be developed. In this context, a new synthesis of pyrano[4,3-*b*]indolones, was realized through $AuCl_3$ catalyzed cycloisomerization of 2-alkynyl- indole-3-carboxylic acids (Scheme 1, eq. 3) and their cytotoxic results against HeLa cells are disclosed in this letter.



Scheme 1. Baldwin's cycloisomerization of acetylenic acids (eq 1) and $AuCl_3$ catalyzed synthesis of isomeric pyranoindolinones (eq 2 and 3)

Our working hypothesis deals with the preparation of indole tethered alkyne substrates, which are capable of efficiently undergoing 6-*endo-dig* cyclization without the formation of 5-

exo-dig species that would preclude any regiochemical control in the course of the reaction.[11] The required precursors were prepared by established procedures (Scheme 2).[5h, 12]



Scheme 2 (a) $POBr_3$ (2.5 equiv.), DMF (10 equiv.), $(CH_2)_2Cl_2$, 0 °C to rt, 24 h (b) Oxone® (1.05 equiv.), MeOH, rt 3 h (c) (for **4a** and **4b**) NaH (2.0 equiv), DMF, 30 min at 0 °C then R^2X (3.0 equiv), 0 °C to rt, 6 h (for, **4c** and **4d**) KOH (3.0 equiv), DMSO, 30 min at 0 °C then R^2X (5.0 equiv), 0 °C to rt, 6 h (d) $Pd(Ph_3P)_4$ (5 mol%), CuI (5 mol%), terminal alkyne, (1.1 equiv), Et_3N, 6 h, rt (e) NaOH (1.5 equiv), MeOH / EtOH / H_2O (3:1:2), 75 °C, 1 h (f) $AuCl_3$ (5 mol%), MeCN, reflux

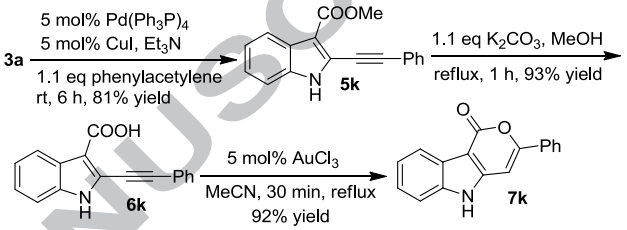
Vilsmeier bromoformylation of oxindole **1a** affords 2-bromo-indole-3-carbaldehyde **2a** in excellent yield.[12a] Oxidative esterification of **2a** with oxone in methanol gave the ester **3a**.[12b] N-alkylation of **3a** was performed with appropriate alkyl halide and base which results in the formation of N-alkyl derivatives **4a-d**.[12c, 12d] By subjecting **4a-d** and terminal acetylenes under standard Sonogashira cross-coupling reaction yields the acetylenic derivatives **5a-j**,[12e] which upon alkaline hydrolysis[3a] of **5a-j** affords the requisite 2-(ethynyl)-indole-3-carboxylic acid **6a-j**. Guidelines for searching of a suitable catalyst for the cyclization of substrates **6a-j** came from our previous studies,[5h] where it was shown that $AuCl_3$ was effective in this sort of transformation. Towards this end, we subjected the acetylenic synthons **6a-j** with 5 mol% of $AuCl_3$ in acetonitrile under refluxing condition. Under this condition, all substrates underwent cyclization and afforded the expected pyranoindolones **7i-7j** in moderate to good yields (Table 1).

Table 1 $AuCl_3$ catalyzed cyclization of **6a** to **7a**

Entry	Substrate	Product[a]	Time (min)	Yield (%)[b]
1	**6a**	**7a**	50	80
2	**6b**	**7b**	60	78
3	**6c**	**7c**	90	75
4	**6d**	**7d**	40	81
5	**6e**	**7e**	90	74
6	**6f**	**7f**	90	73
7	**6g**	**7g**	90	67
8	**6h**	**7h**	90	65
9	**6i**	**7i**	90	59
10	**6j**	**7j**	90	62

[a] All the Products were characterized by IR, ^{1}H NMR, ^{13}C NMR and MS
[b] Isolated yield after column chromatography

It is noteworthy to mention that precursors, **6a-j** led to reasonable conversion with only an increase of the reaction time and this can be attributed to the reduced electrophilicity of carboxylic acid in C3-indole. The low yield observed in compounds **6i** and **6j** can be rationalized by the decrease in Lewis acidity of the catalyst by coordinating with the hydroxyl function and eventually the catalytic efficiency of the overall process. In agreement to our previous results,[5h] the cycloisomerization follows 6-*endo-dig* regiochemistry[13a] leading to δ-lactone and no γ-lactone was observed as evidenced by crude NMR analysis. This observation was in sharp disagreement with other gold catalysis protocol, where γ-lactone was formed exclusively.[4c-4f] This can be ascribed to the energetic inaccessibility or greater strain of 5-5 ring formation over 5-6 ring formation. The formation of δ-lactone ring in all compounds was ascertained by stretching band between 1695 and 1721 cm^{-1} in their IR spectrum. In ^{1}H NMR spectrum a singlet between δ_H 5.86 and 6.81 ppm were observed, characteristic of the C4-hydrogen of **7a-j**. Moreover all compounds exhibited two characteristic peaks in their ^{13}C NMR spectrum at δ_C = 97.9-100.1 and 163.5-168.5 ppm, confirming the presence of C4-carbon and lactone carbonyl carbon of **7a-j** respectively.

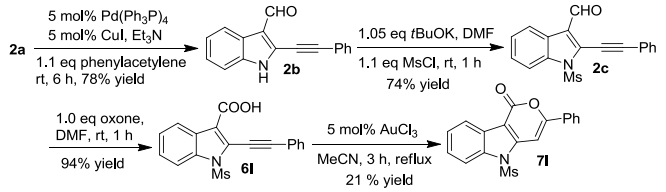


Scheme 3 Synthesis and Cyclization of N-unprotected indolyl alkyne **6k**

In an effort to showcase the tolerance of our chemistry towards challenging N-unprotected indoles, we next investigated the cyclization of substrate **6k** devoid of any substitution at the indole nitrogen atom (Scheme 3). The synthesis of **6k** was executed essentially according to the strategy used for the synthesis of **6a-j**. Gratifyingly, a smooth cyclization of **6k** to product **7k** was observed with an excellent yield, suggesting that a free -NH group was indeed tolerated under our reaction conditions. We consider $AuCl_3$ only to be a precatalyst and we do not know whether the catalytically active species is Au(III) or Au(I), but it should be an electrophilic gold species. We occasionally observed the precipitation of gold in the form of gold mirror but this always occurred after the reaction was complete. The possibility of participation of Au(I) as catalytic species, (via redox chemistry) was ruled out by performing a reaction with **6k** using 5 mol% of AuCl in acetonitrile under reflux, which led to the formation of only 20% of the product **7k**. We reasoned out that AuCl could not be electrophilic enough to allow for cycloisomerization, thus demonstrating that the catalytic activity of $AuCl_3$ is superior to that of AuCl in this reaction. It is pertinent to note that, our approach is devoid of any Ag-additive; the Reader will be reminded that these air-, light- and moisture-sensitive Ag salts of type AgX (X = BF_4, SbF_6, PF_6, NTf_2) are usually employed to generate the cationic Au(I) species from LAuCl (L = phosphine or NHC).[14a]

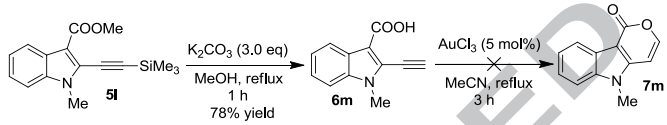
We were also intrigued by the prospect of applying this methodology to substrate possessing a labile electron withdrawing group at the nitrogen atom (Scheme 4). The precursor required for this study was prepared starting from the Sonogashira coupling of **2a** to give **2b**. Subsequent mesylation, where *t*BuOK was used as base, delivered the mesyl aldehyde **2c** in 74% yield. A clean oxidation of the aldehyde **2c** was conducted with oxone to afford the acid precursor **6l**. Subjecting **6l** under our standard condition led to a sluggish reaction and affords only 21% yield of the product **7l**. This diminution in yield could be attributed to the electron withdrawing nature of mesyl group which decreases electron density of the triple bond, thus lowering the coordination ability of the acetylenic moiety towards Au(III). Results from Scheme 1 to 3 suggested that

either free NH or NR (where, R is any electron releasing group) of indole is necessary to realize effective cyclization, whereas a deactivating group at the nitrogen reduces the efficiency of the cyclization.



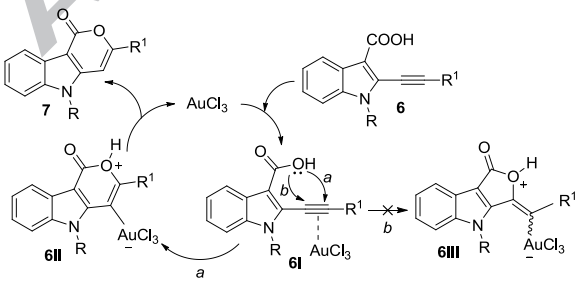
Scheme 4 Synthesis and cyclization of N-protected indolyl alkyne **6l**

Up to this point, we merely uncovered the scope of substrates possessing internal alkynes. To gain insight into the influence of the electronic nature of alkyne, a control experiment with substrate possessing terminal alkyne was envisaged. For this study, the requisite alkyne **6m** was prepared through K_2CO_3 promoted tandem desilylation/hydrolysis of silyl ester **5l** (Scheme 5). By subjecting **6m** under our reaction conditions, no ring-closing event to product **7m** was observed and almost 80% of the starting material **6m** was recovered. Such evidence can be ascribed to the reduced electrophilicity of the terminal sp-carbon of the alkyne. Therefore, the only possibility for the carboxyl function is to attack the remote sp-carbon of the Au-complexed alkyne, but this scenario would lead to 5-5 ring fusion, which in the present case is energetically unfavorable. It is also worth noting that this substrate did not afforded the lactone dimer neither through Glaser-type homocoupling, as it was the case observed with several terminal alkynes under Au(III)-catalysis[3d] or through oxidative coupling of the vinylgold-intermediates.[14b]



Scheme 5 Reaction with terminal alkyne **6m**

A reaction mechanism for the formation of **7** was proposed (Scheme 6).[14c] According to which, π-electrophilic $AuCl_3$ activates the C-C triple bond of **6** leading to the π-complex **6I**. As per Baldwin's rule, the later could undergo either 6-*endo-dig* (via path a) or 5-*exo-dig* (via path b) cyclization to form complexes **6I** and **6III** respectively. On the grounds of energetic inaccessibility of 5-5 ring formation, the regiochemistry would be directed towards 6-*endo-dig* (against 5-*exo-dig*) to form the cyclized intermediate **6II**. Protodeauration, where the labile C-Au bond of intermediate **6II**[14d,14e] was replaced by C-H bond results in the formation of product **7** along with the regeneration of $AuCl_3$.



Scheme 6 Plausible mechanism for the $AuCl_3$ catalyzed formation of **7**

In pursuance of our on-going project on bio-active heterocycles,[3o, 5h, 15] an attempt has been made to evaluate the cytotoxicity of compounds (**7a-7k**) against human adenocarcinoma cell lines (HeLa) by MTT assay.[16] The cytotoxic results were compared with reference drug *cis*-platin, which showed an IC_{50} value of 0.08 μM.[17] The tested compounds exhibited maximum cytotoxicity against HeLa cells at a concentration of 0.69 to 2.25 μM (Table 2).[18] From the analysis of the observed data, it was found that compound **7d** possessing C3-phenyl and N-benzyl substituent showed highest activity (IC_{50} = 0.69 μM). Compound **7c** which contains butyl chain at C3 and indolic nitrogen emerged as the second most active in the series (IC_{50} = 1.11 μM). However, replacement of N-butyl by a small group like methyl (**7a**) marginally reduced the inhibitory potency to 1.24 μM. By increasing the chain length to ethyl at the nitrogen atom (**7b**), a slight decrease in activity was observed (IC_{50} = 1.41 μM). Switching from phenyl to aliphatic chains such as butyl and pentyl as a C3-substituent (**7e-h**) exhibited only moderate potency with the IC_{50} values ranging between 1.63 and 1.92 μM. Compounds possessing tertiary and primary hydroxyl (**7i** and **7j**) emerged as the least active among the tested series (IC_{50} = 2.02 and 2.25 μM respectively) suggesting the intolerance of polar substituent at the C3-site. Likewise, compound **7k**, possessing no substitution at indolic nitrogen exhibited poor cytotoxicity among the screened series. These qualitative assessments revealed that the presence of C3-phenyl substituent (as in **7a-d**) is essential for exhibiting good inhibitory potency.

Table 2 Cytotoxicity of compounds **7a-7j** against HeLa cells

Entry	Compound	IC_{50} (μM)
1	**7a**	1.24
2	**7b**	1.41
3	**7c**	1.11
4	**7d**	0.69
5	**7e**	1.92
6	**7f**	1.89
7	**7g**	1.75
8	**7h**	1.63
9	**7i**	2.02
10	**7j**	2.25
11	**7k**	2.55
12	*cis*-platin	0.08

In pharmaceutical drug design, the discovery of small molecules that predominantly undergo non-covalent interactions such as hydrogen bonding, van der Waals, π-π and π-cationic interactions in protein-ligand binding is an important concept.[19] This *in silico* approach involves the docking of synthesized compounds into the active site of the 3D structure of the target, followed by the calculation of free energy of binding (FEB) of the protein-ligand complex. The binding mode of the potent inhibitors was investigated using AutoDock Tools (ADT) version 1.5.6 and AutoDock version 4.2.5.1 docking program to rationalize the pharmacological results.[20] To gain insights of the observed activity, we docked all the compounds to Vaccinia H1-Related (VHR) Phosphatase receptor (PDB ID: 3F81) crystal structures available in the Protein Data Bank. A link between VHR and cervical cancer was well established. Compared to normal keratinocytes, VHR protein levels are found to be up regulated in several cervix cancer cell lines including human papillomavirus (CaSki, HeLa, SiHa, HT3 and C33). Biopsies of the primary cervix cancer, squamous intraepithelial lesions and squamous cell carcinomas of the uterine cervix revealed the higher expression levels of VHR protein level. This clearly suggests that in the treatment of cervical cancer, VHR might be a promising drug target and VHR inhibiting small-molecules could be a potential drug to cure the cervical cancer.[21] To start with, the reproducibility of docking calculations was verified by extracting the co-crystallized ligand from the complexes and submitted for one-ligand run calculation. This reproduced top scoring

conformation falling within root-mean-square deviation (RMSD) value of 1.04 Å with bound X-ray conformation for 3F81, suggesting this method is valid enough to be used for docking studies of other compounds (Figure 1). Docking simulation of all the synthesized compounds was performed in the same active site using the same protocol used for the validation study (Figure 2). For each of the test molecules, dockings were performed by taken into 2.5 million energy evaluations. The conformations of docked ligand with VHR receptor were analyzed in terms of energy, hydrogen bonding, hydrophobic and π-π interaction. The final coordinates of the ligand and receptor were saved after the clear analysis of ligand-receptor interactions. To investigate the interactions of ligand and receptor simulated conformations output was exported to PyMOL software. The free energy of binding (FEB) of all compounds were calculated from the docking scores (Table 3).

Table 3 FEB values of compounds on VHR phosphatase receptor

Entry	Compound	FEB (kcal/mol)[a]
1	**7a**	-5.89
2	**7b**	-5.86
3	**7c**	-6.10
4	**7d**	-7.27
5	**7e**	-5.17
6	**7f**	-5.00
7	**7g**	-6.31
8	**7h**	-6.47
9	**7i**	-6.77
10	**7j**	-6.51
11	**7k**	-5.89

[a]Free energy of binding (PDB ID: 3F81)

The results revealed that all the docked compounds bind with the receptor and exhibits free energy of binding value between -5.00 and -7.27 kcal/mol. All the compounds binds in the active site and the simulated conformation exhibits various interactions with 16 amino acids namely LEU-25, PRO-26, PHE-68, MET-69, ASP-92, CYS-124, ARG-125, GLU-126, GLY-127, TYR-128, SER-129, ARG-130, ARG-158, GLY-161, PRO-162 and ASN-163 with non-covalent interactions such as hydrophobic, hydrophilic, π-π interaction and hydrogen bonding. Among all compounds docked, **7d** exhibits high binding with 3F81 receptor and forms hydrogen bonding with GLY-161 amino acid which resulted in binding energy of -7.27 kcal/mol (Figure 3). The benzyl moiety exhibits hydrophobic interaction with GLY-126, in addition to the CH-π interaction with the phenyl ring of TYR-128. It is to be noted that compound **7d** with highest binding energy (-7.27 kcal/mol) did exhibited significant IC_{50} value (0.69 μM), thus establishing a correlation with the biological results.

In summary, syntheses of pyrano[4,3-*b*]indol-1(5*H*)-ones through gold(III)-catalyzed 6-*endo*-*dig* cycloisomerization of 2-alkynyl-indole-3-carboxylic acids have been developed. The current method has promising advantage toward practical uses because of the high regioselectivity, short reaction time, high atom-economy, modest chemical yield and functional group compatibility. In view of a large number of bioactivities involving fused-indole scaffolds, we screened the synthesized compounds for cytotoxicity against HeLa cells. The results of which indicated that compound **7d** emerged as the most active with an IC_{50} of 0.69 μM (FEB = -7.27 kcal.mol). We expect that these potential special structures will have wide applicability in medicinal chemistry. Further studies to extend the scope of this procedure to other heterocycles and DFT computational studies are underway in our laboratory and will be reported shortly.

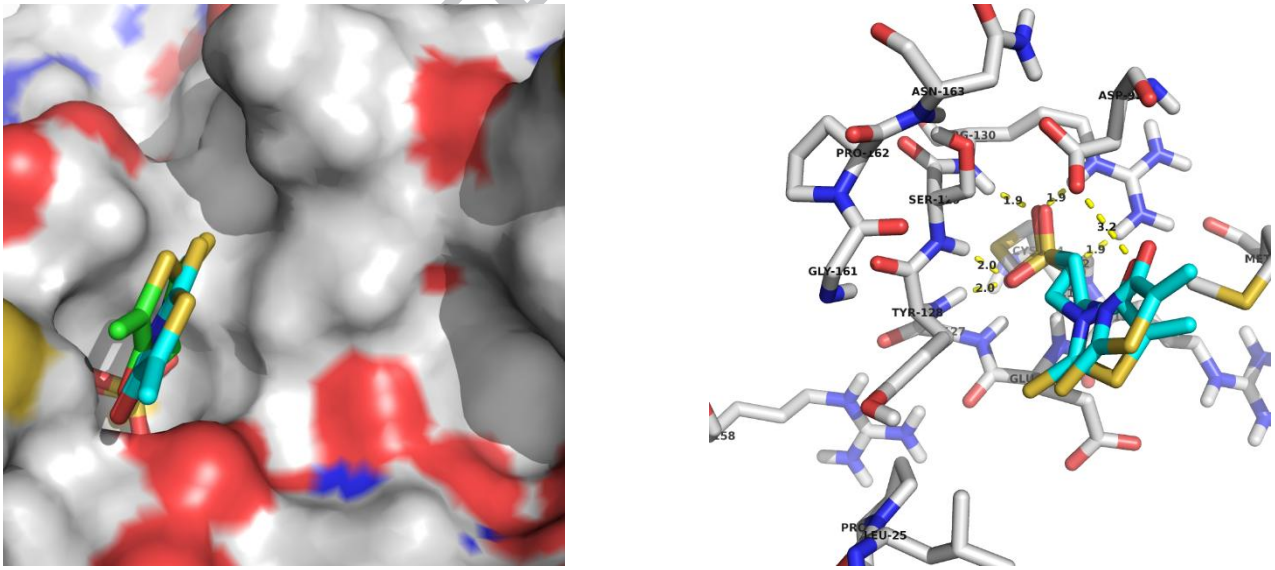


Figure 1 Validation using crystallized and docked ligand with 3P9J receptor

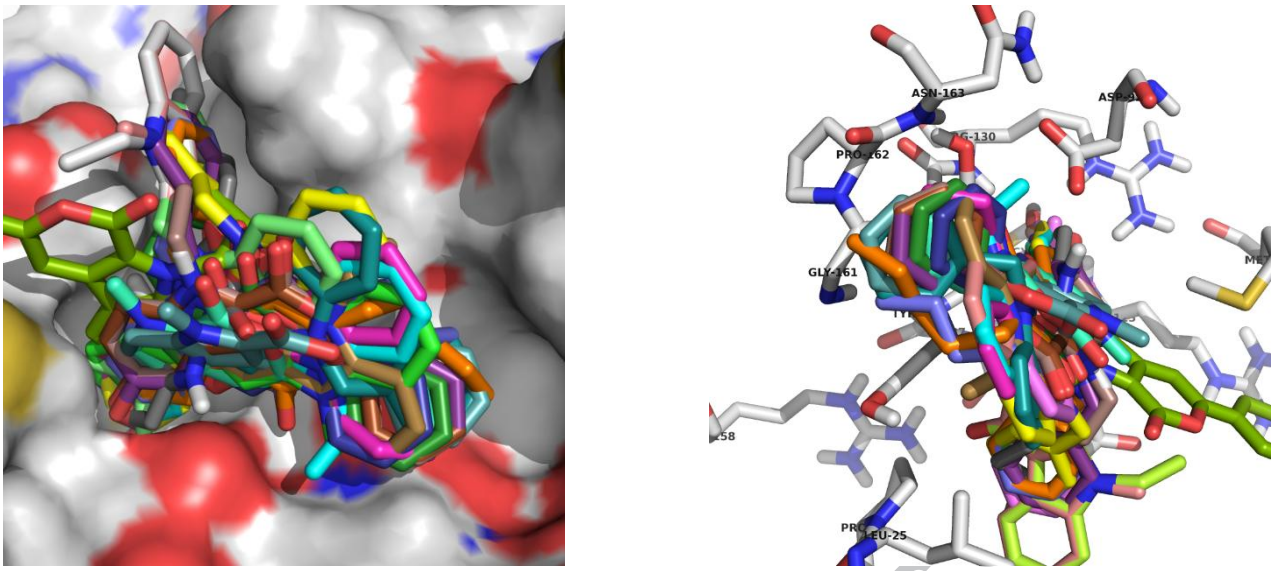


Figure 2 Docking mode of all the compounds in the active site of 3P9J receptor

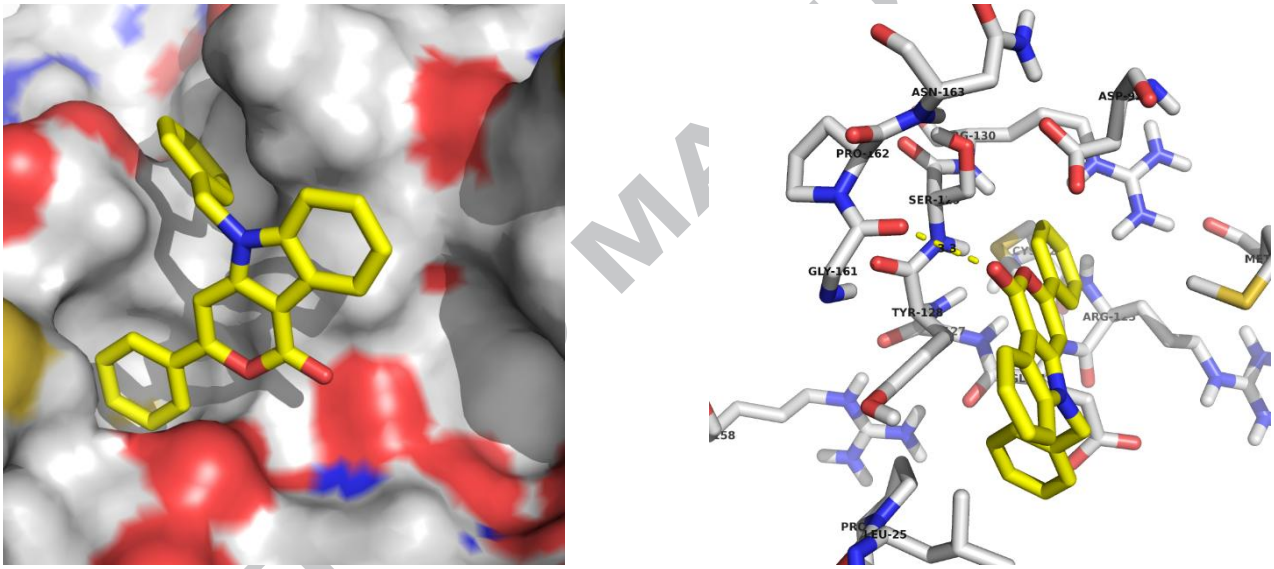


Figure 3 Docking mode of the most active compounds **7d** in the active site of 3P9J

Acknowledgments

The work has been financially supported by a fast track grant for young scientists (Grant no: SERB/F/5666/2015-16) from Science and Engineering Research Board (SERB), India. C. P. is grateful to Dr. Vijayamohanan K. Pillai, Director, CSIR-CECRI for allowing to publish this work and Dr. D. Jeyakumar, Head, Functional Materials Division, CSIR-CECRI for providing laboratory and analytical facilities.

Supplementary data

Experimental procedure for the synthesis of starting materials, cytotoxicity evaluation, molecular docking, ^{1}H NMR, ^{13}C NMR and mass spectra were provided in the supplementary material.

References and notes

1 (a) Whyte, A. C.; Gloer, J. B.; Scott, J. A.; Mallock, D. *J. Nat. Prod.* **1996**, *59*, 765; (b) Furuta, T.; Fukuyama, Y.; Asakawa, Y. *Phytochemistry* **1986**, 25, 517; (c) Bürki, N.; Michel, A.; Tabacchi, R. *Phytopathol. Mediterr.* **2003**, *42*, 191; (d) Yoshikawa, M.; Matsuda, H.; Shimoda, H.; Shimada, H.; Harada, E.; Naitoh, Y.; Miki, A.; Yamahara, J.; Murakami, N. *J. Chem. Pharm. Bull.* **1996**, *44*, 1440.

2 (a) Trani, A.; Dallanoce, C.; Panzone, G.; Ripamonti, F.; Goldstein, B. P.; Ciabatti, R. *J. Med. Chem.* **1997**, *40*, 967; (b) Lee, J. H.; Park, Y. J.; Kim, H. S.; Hong, Y. S.; Kim, K. W.; Lee, J. J. *J. Antibiot.* **2001**, *54*, 463. (c) Matsuda, H.; Shimoda, H.; Yamahara, J.; Yoshikawa, M. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 215.

3 (a) Marchal, E.; Uriac, P.; Legouin, B.; Toupet, L.; Weghe, P. v. d. *Tetrahedron* **2007**, *63*, 9979. (b) Biagetti, M.; Bellina, F.; Carpita, A.; Stabilea, P.; Rossi, R. *Tetrahedron* **2002**, *58***,** 5023; (c) Bianchi, G.; Chirani, M.; Marinelli, F.; Rossi, L.; Arcadi, A. *Adv. Synth. Catal.* **2010**, *352***,** 136; (d) Harkat, H.; Dembelé, A. Y.; Weibel, J.-M.; Blanc, A.; Pale, P. *Tetrahedron* **2009**, *65*, 1871; (e) Harkat, H.; Weibel, J-M.; Pale, P. *Tetrahedron Lett.* **2006**, *47*, 6273; (f) Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P.; Mannina, L. *Tetrahedron* **2003**, *59*, 2067; (g) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936; h) Liang, Y.; Xie, Y-X.; Li, J-H. *Synthesis* **2007**, 400; (i) Sakamoto, T.; An-Naka, M.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1986**, *34***,** 2754; (j) Peuchmaur, M.; Lisowski, V.; Gandreuil, C.; Maillard, L. T.; Martinez, J.; Hernandez, J-F. *J. Org. Chem.* **2009**, *74***,** 4158; (k) Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439; (l) Liao, H-Y.; Cheng, C-H. *J. Org. Chem.* **1995**, *60***,** 3711; (l) Bras, G. L.; Hamze, A.; Messaoudi, S.; Provot, O.; Calvez, P-B. L.; Brion, J-D.; Alami, M.

Synthesis **2008**, 1607.; (m) Sashida, H.; Kawamukai, A. *Synthesis* **1999** 1145. (n) Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. *Org. Lett.* **2006**, *8***,** 5517.; (o) Praveen, C.; Dheenkumar, P.; Perumal, P. T. *J. Chem. Sci*. **2013**, *125*, 71; (p) Mehta, S.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2009**, *74***,** 1141; (q) Woon, E. C. Y.; Dhami, A.; Mahon, M. F.; Threadgill, M. D. *Tetrahedron* **2006**, *62***,** 4829; (r) Roy, S.; Roy, S.; Neuenswander, B.; Hill, D.; Larock, R. C. *J. Comb. Chem.* **2009**, *11***,** 1128; (s) Subramanian, V.; Batchu, V. R.; Barange, D.; Pal, M. *J. Org. Chem.* **2005**, *70***,** 4778; (t) Raju, S.; Batchu, V. R.; Swamy, N. K.; Dev, R. V.; Sreekanth, B. R.; Babu, J. M.; Vyas, K.; Kumar, P. R.; Mukkanti, K.; Annamalai, P.; Pal, M. *Tetrahedron* **2006**, *62***,** 9554; (u) Oliver, M. A.; Gandour, R. D. *J. Org. Chem.* **1984**, *49*, 558; (v) Yao, T.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 7401; (w) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron* **2001**, *57*, 2857; (x) Hellal, M.; Bourguignon, J.-J.; Bihel, F. J.-J. *Tetrahedron Lett.* **2008**, *49*, 62.

4 (a) Inack-Ngi, S.; Rahmani, R.; Commeiras, L.; Chouraqui, G.; Thibonnet, J.; Duchêne, A.; Abarbri, M.; Parrain, J-L. *Adv. Synth. Catal.* **2009**, *351*, 779; (b) Zhou, L.; Jiang, H-F. *Tetrahedron Lett.* **2007**, *48*, 8449. (c) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112; (d) Genin, E.; Toullec, P. Y.; Marie, P.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *ARKIVOC* **2007**, *v*, 67; (e) Tomás-Mendivil, E.; Toullec, P. Y.; Díez, J.; Conejero, S.; Michelet, V.; Cadierno, V. *Org. Lett.* **2012**, *14*, 2520. (f) Neaţu, F.; Li, Z.; Richards, R.; Toullec, P. Y.; Genêt, J.-P.; Dumbuya, K.; Gottfried, J. M.; Steinrück, H. P.; Pârvulescu, V. I.; Michelet, V. *Chem.-Eur. J.* **2008**, *14*, 9412.

5 (a) Praveen, C.; Kiruthiga, P.; Perumal, P. T. *Synlett* **2009**, 1990; (b) Praveen, C.; Jegatheesan, S.; Perumal, P. T. *Synlett* **2009**, 2795; (c) Praveen, C.; Perumal, P. T. *Synthesis* **2016**, *48*, 855; (d) Praveen, C.; Kalyanasundaram, A.; Perumal, P. T. *Synlett* **2010** 777; (e) Praveen, C.; Sagayaraj, Y. W.; Perumal, P. T. *Tetrahedron Lett.* **2009**, *50*, 644; (f) Praveen, C.; Karthikeyan, K.; Perumal, P. T. *Tetrahedron* **2009**, *65*, 9244. (g) Praveen, C.; Perumal, P. T. *Synlett* **2011**, 521; (h) Praveen, C.; Ayyanar, A.; Perumal, P. T. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4170; (i) Jeyaveeran, J. C.; Praveen, C.; Arun, Y.; Prince, A. A. M.; Perumal, P. T. *J. Chem. Sci.* **2016**, *128*, 73. (j) Praveen, C.; Perumal, P. T. *Chin. J. Catal*. **2016**, *37*, 288.

6 (a) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem. Int. Ed*. **2006**, *45*, 7896; (b) Rudolph, M.; Hashmi, A. S. K. *Chem. Commun.* **2011**, *47*, 6536.

7 For the first use of $AuCl_3$ in homogeneous gold catalysis, see: (a) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc*. **2000**, *122*, 11553; (b) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem. Int. Ed*. **2000**, *39*, 2285.

8 (a) Shimizu, M.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 3478; (b) Nandi, D.; Ghosh, D.; Chen, S.-J.; Kuo, B.-C.; Wang, N. M.; Lee, H. M. *J. Org. Chem*. **2013**, *78*, 3445.

9 For the Pd-catalyzed synthesis of isomeric pyranoindolones, see: Suresh, R. R.; Swamy, K. C. K. *J. Org. Chem.* **2012**, *77*, 6959.

10 (a) Ngi, S.; Guilloteau, V.; Abarbri, M.; Thibonnet, J. *J. Org. Chem*. **2011**, *76*, 8347; (b) Xin, Z.; Lescot, C.; Friis, S. D.; Daasbjerg, K. ; Skrydstrup, T. *Angew. Chem. Int. Ed*. **2015**, *54*, 6862

11 For other regiochemical switches in homogeneous gold catalysis, see: Hashmi, A. S. K.; Schuster, A. M.; Gaillard, S.; Cavallo, L.; Poater, A.; Nolan, S. P. *Organometallics* **2011**, *30*, 6328.

12 (a) Somei, M.; Sayama, S.; Naka, K.; Shinmoto, K.; Yamada, F. *Heterocycles* **2007**, *73*, 537; (b) Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett*. **2003**, *5*, 1031; (c) Sechi, M.; Derudas, M.; Dallocchio, R.; Dessí, A.; Bacchi, A.; Sannia, L.; Carta, F.; Palomba, M.; Ragab, O.; Chan, C.; Shoemaker, R.; Sei, S.; Dayam, R.; Neamati, N. *J. Med. Chem.* **2004**, *47*, 5298; (d) Tsotinis, A.; Afroudakis, P. A.; Davidson, K.; Prashar, A.; Sugden, D. *J. Med. Chem.* **2007**, *50*, 6436; (e) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, *16*, 4467.

13 For the same regioselectivity in the cyclization of 2-alkynylbenzyl alcohols, see: Hashmi, A. S. K.; Schäfer, S.; Wölfle, M.; Gil, C. D.; Fischer, P.; Laguna, A.; Blanco, M. C.; Gimeno, M. C. *Angew. Chem. Int. Ed***.** **2007**, *46*, 6184.

14 (a) Lu, Z.; Han, J.; Hammond, G. B.; Xu, B. *Org. Lett***.** **2015**, *17*, 4534; (b) Hashmi, A. S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem***.** **2006**, 1387. (c) Hashmi, A. S. K. *Angew. Chem. Int. Ed***.** **2010**, *49*, 5232 ; (d) Hashmi, A. S. K.; Schuster, A. M.; Rominger, F. *Angew. Chem. Int. Ed***.** **2009**, *48*, 8247 ; (e) Hashmi, A. S. K. *Gold Bull***.** **2009**, *42*, 275.

15 (a) Praveen, C.; Narendiran, S ; Dheenkumar, P.; Perumal, P. T. *J. Chem. Sci*. **2013**, *125*, 1543 ; (b) Praveen, C.; Iyyappan, C.; Girija, K.; Kumar, K. S.; Perumal, P. T. *J. Chem. Sci*. **2012**, *124*, 451; (c) Praveen, C.; Ayyanar, A.; Perumal, P. T. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 4072; (d) Praveen, C.; Dheenkumar, P.; Muralidharan, D.; Perumal, P. T. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7292; (e) Parthasarathy, K.; Praveen, C.; Balachandran, C.; Kumar, P. S.; Ignacimuthu, S.; Perumal, P. T. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 2708; (f) Parthasarathy, K.; Praveen, C.; Kumar, P. S.; Balachandran, C.; Perumal, P. T. *RSC Advances* **2015**, *5*, 15818; (g) Praveen, C.; Nandakumar, A.; Dheenkumar, P.; Muralidharan, D.; Perumal, P. T. *J. Chem. Sci*. **2012**, *124*, 609.

16 Mossman, T. *J. Immunol. Methods* **1983**, *65*, 55.

17 Based on our previous study, we chose *cis*-platin as the reference drug, see Ref. 5h.

18 It is to be noted that not all α,β-unsaturated carbonyl compounds lacks in cyto-selectivity, see: Nakayachi, T.; Yasumoto, E.; Nakano, K.; Morshed, S. F. MD.; Hashimoto, K.; Kikuchi, H.; Nishikawa, H.; Kawase, M.; Sakagami, H. *Anticancer Research* **2004**, *24*, 737.

19 Williams, D. H.; Stephens, E.; O'Brien, D. P.; Zhou, M. *Angew. Chem. Int. Ed*. **2000**, *43*, 6596.

20 (a) Morris, G. M.; Huey, R.; Lindstrom, W.; Sanner, M. F.; Belew, R. K.; Goodsell, D. S.; Olson, A. J. *J. Comput. Chem.* **2009**, *30*, 2785; (b) Sanner, M. F. *J. Mol. Graphics Mod*. **1999**, *17*, 57.

21 Wu, S.; Vossius, S.; Rahmouni, S.; Miletic, A. V.; Vang, T.; Vazquez-Rodriguez, J.; Cerignoli, F.; Arimura, Y.; Williams, S.; Hayes, T.; Moutschen, M.; Vasile, S.; Pellecchia, M.; Mustelin, T.; Tautz, L. *J. Med. Chem.* **2009**, *52*, 6716.